What endpoints should be used in clinical trials of HAP and VAP?

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Competing interests:

Dr. Chastre has received speaker honoraria and/or consulting fees from Nektar-Bayer, Pfizer, Kalobios-Sanofi-Aventis, Johnson & Johnson, Janssen-Cilag, Astellas, Kenta, and Brahms.

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Outline:

1. What should be the primary efficacy variable?
2. Which secondary endpoints?
3. How to define clinical success (failure) at TOC?

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EXECUTIVE SUMMARY SUPPLEMENT ARTICLE

Workshop on Clinical Trials of Antibacterial Agents for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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SUPPLEMENT ARTICLE POSITION PAPER

Recommended Design Features of Future Clinical Trials of Antibacterial Agents for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

Brad Spellberg[1,2] and George Talbot,[3] for the Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and Society of Critical Care Medicine

[1]Division of General Internal Medicine, Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles (UCLA) Medical Center, and [2]David Geffen School of Medicine at UCLA, Los Angeles, and [3]Talbot Advisors, Wayne, Pennsylvania

Guidance for Industry

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

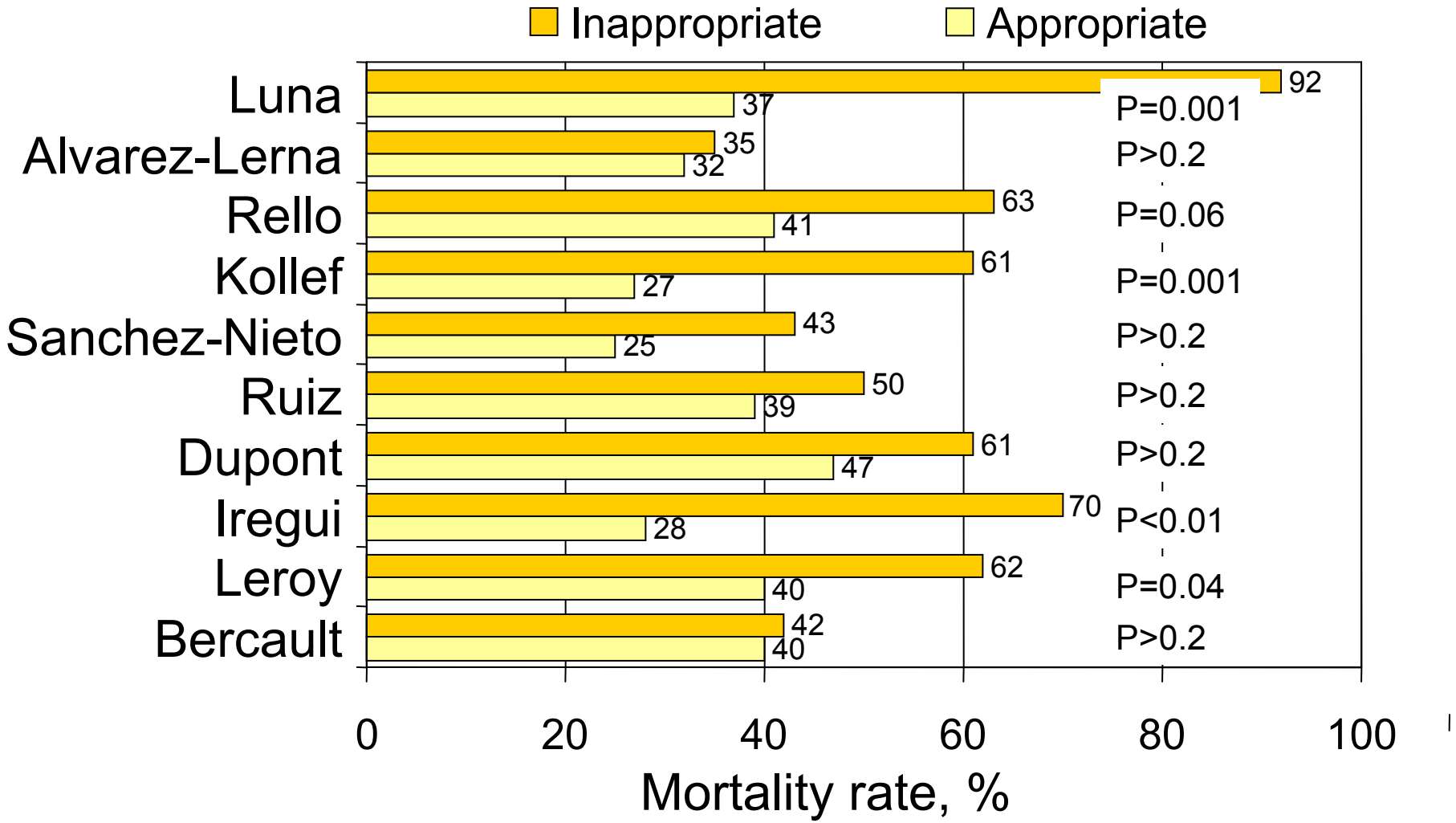
Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

What should be the primary efficacy variable?

- Most previous randomized, comparator-controlled trials in HAP/VAP have used **“Clinical cure rate”** at TOC as primary endpoint.
- Definition of clinical cure was frequently investigator-based and rather loose, based on subjective criteria:
  - Complete resolution of all signs and symptoms
  - Improvement or lack of progression of all abnormalities on x-ray by the 7 to 21 d TOC visit.

Mortality Associated with Initial Inappropriate Therapy in Patients with VAP



"PLACEBO" ALL-CAUSE MORTALITY RATE

- **Relevant data sources**
  - No placebo studies
  - No dose-ranging studies
  - Two retrospective studies of hospitalized patients with *P. aeruginosa* pneumonia that included patients left untreated
  - 12 non-randomized, observational cohort studies that assessed all-cause mortality in relation to the adequacy of the initial antibacterial treatment

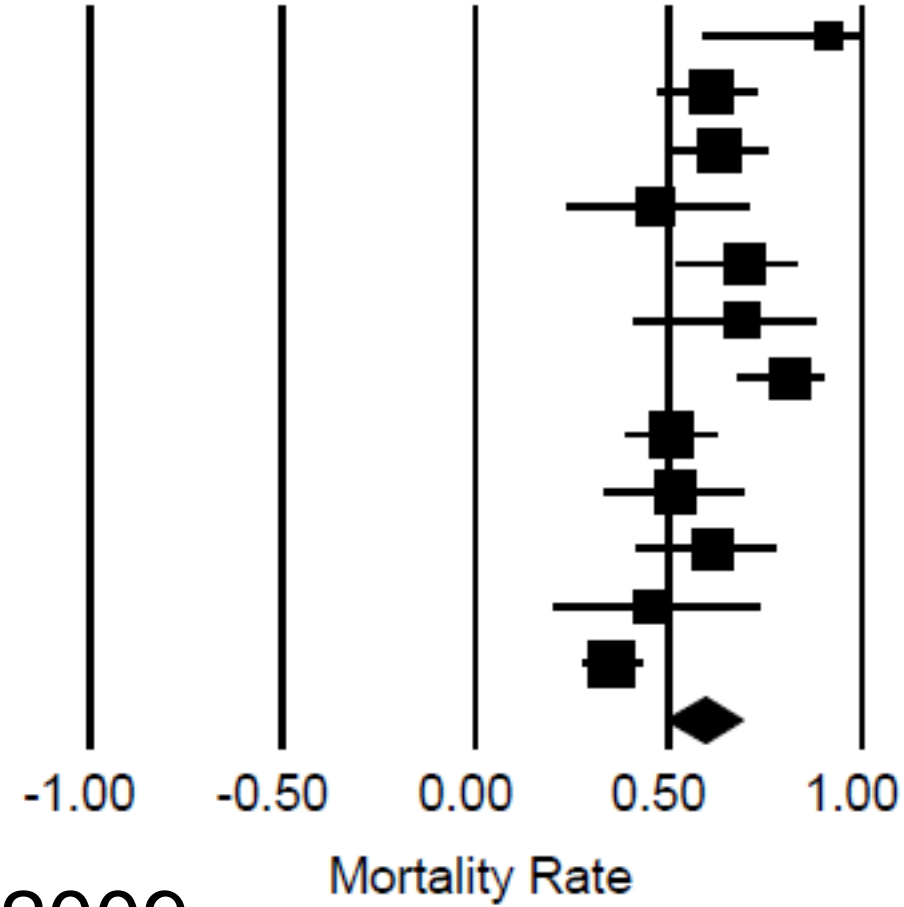
A. Sorbello, FDA Workshop, 2009

"PLACEBO" ALL-CAUSE MORTALITY RATE

Study	Mortality rate	Lower limit	Upper limit
A	0.917	0.587	0.988
B	0.608	0.469	0.731
C	0.635	0.497	0.753
D	0.467	0.241	0.707
E	0.697	0.523	0.829
F	0.692	0.409	0.880
G	0.816	0.683	0.902
H	0.507	0.391	0.623
I	0.519	0.336	0.696
J	0.615	0.421	0.779
K	0.455	0.203	0.732
L	0.349	0.276	0.430
Random	0.597	0.493	0.692

Statistics for each study

Mortality rate and 95% CI



A. Sorbello, FDA Workshop, 2009

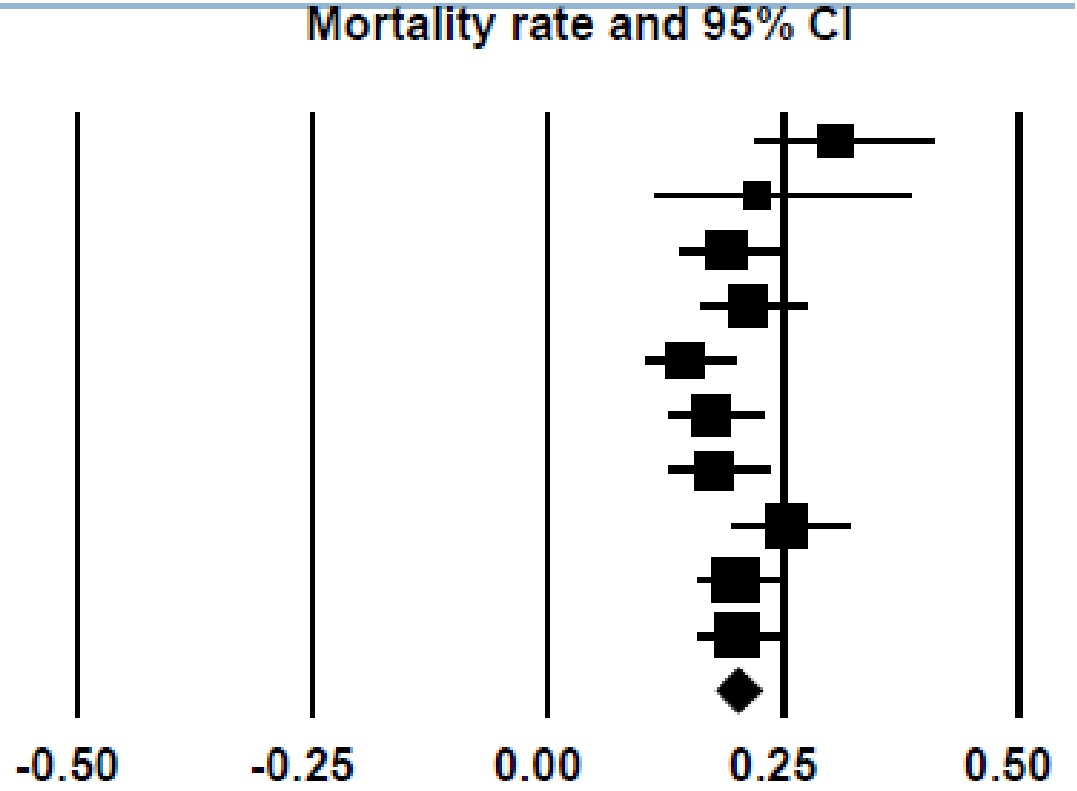
ACTIVE CONTROL ALL-CAUSE MORTALITY RATE

- **Relevant data sources**
  - No placebo-controlled studies
  - 9 randomized, prospective, comparator-controlled clinical efficacy studies involving the following drugs:
    - Piperacillin/tazobactam
    - Imipenem
    - Ceftazidime
    - Levofloxacin
    - Ciprofloxacin
    - Vancomycin
    - Linezolid

A. Sorbello, FDA Workshop, 2009

ACTIVE CONTROL ALL-CAUSE MORTALITY RATE

Reference #	Mortality rate	Lower limit	Upper limit
[5] P/T/A	0.307	0.220	0.410
[5] Cef/A	0.222	0.115	0.385
[6] Imi	0.190	0.141	0.250
[6] Cip	0.213	0.162	0.275
[7] Imi iv/Cip po	0.147	0.106	0.200
[7] Lev iv/Lev po	0.173	0.128	0.228
[8] Lzd	0.177	0.131	0.236
[8] Van	0.254	0.197	0.320
[9] Lzd	0.199	0.159	0.247
[9] Van	0.202	0.160	0.251
Random	0.202	0.180	0.228

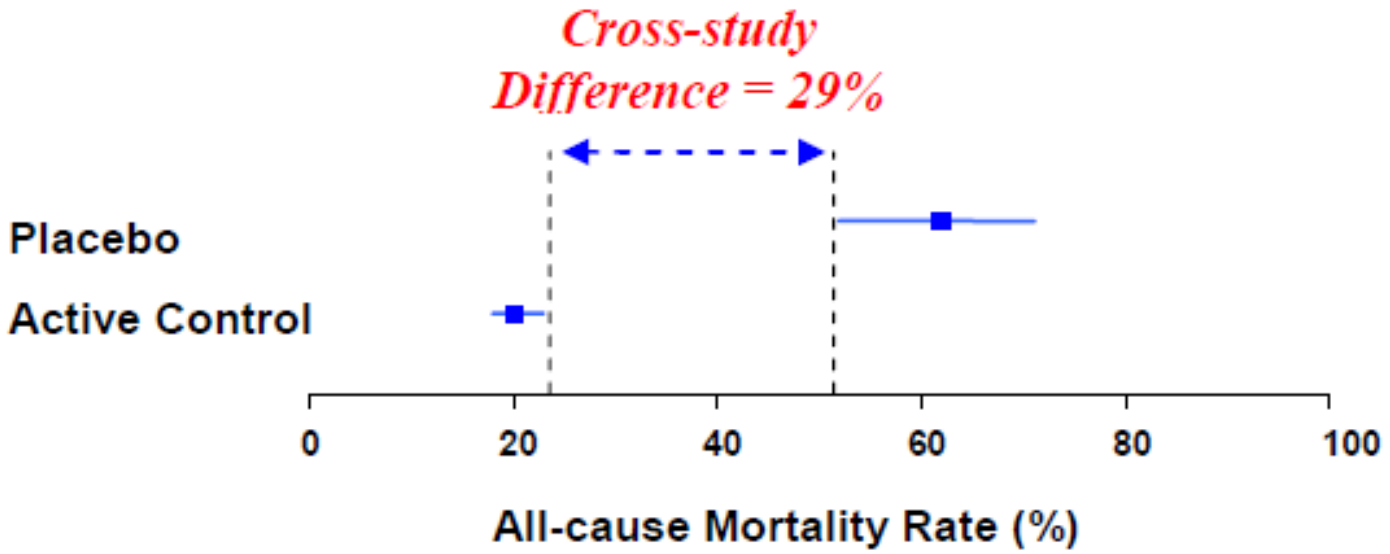


AC all-cause mortality rate estimate: 20% (18%, 23%)

A. Sorbello, FDA Workshop, 2009

DETERMINATION OF M1

- **M1 = treatment effect of Active Control (AC) over "placebo"**
- **Cross-study difference in all-cause mortality rates between AC and "placebo" = 29%:**
  - based on comparison of 95% CIs, where the lower bound of the 95% CI for "placebo" was 52% and the upper bound of the 95% CI for AC was 23%



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What should be the primary efficacy variable for HAP/VAP?

- Clinical trials should be designed to demonstrate a **treatment effect** of the new antibacterial agent **at least noninferior** to available comparators, using **all-cause mortality** within 28 d after randomization as primary endpoint (safety margin ≤10%).
- Trials should be **randomized**, **double-blind**, and active **comparator-controlled**.
- Trial population should include patients who are sufficiently ill (**28-day predicted mortality ≥20%**).
- Primary analysis population should be patients with a **microbiologically confirmed** bacterial etiology.

Secondary Endpoints

- **Clinical response at TOC**
- All cause mortality rate at days 14
- Number of MV-free days at days 28
- Number of antibiotics-free days at days 28
- CPIS and PCT changes from Day 1 to TOC
- Clinical relapse rates at Day 28
- Clinical and microbiological response by baseline isolate
- Safety and tolerability

Epidemiology and outcomes of ventilator-associated pneumonia in a large US database

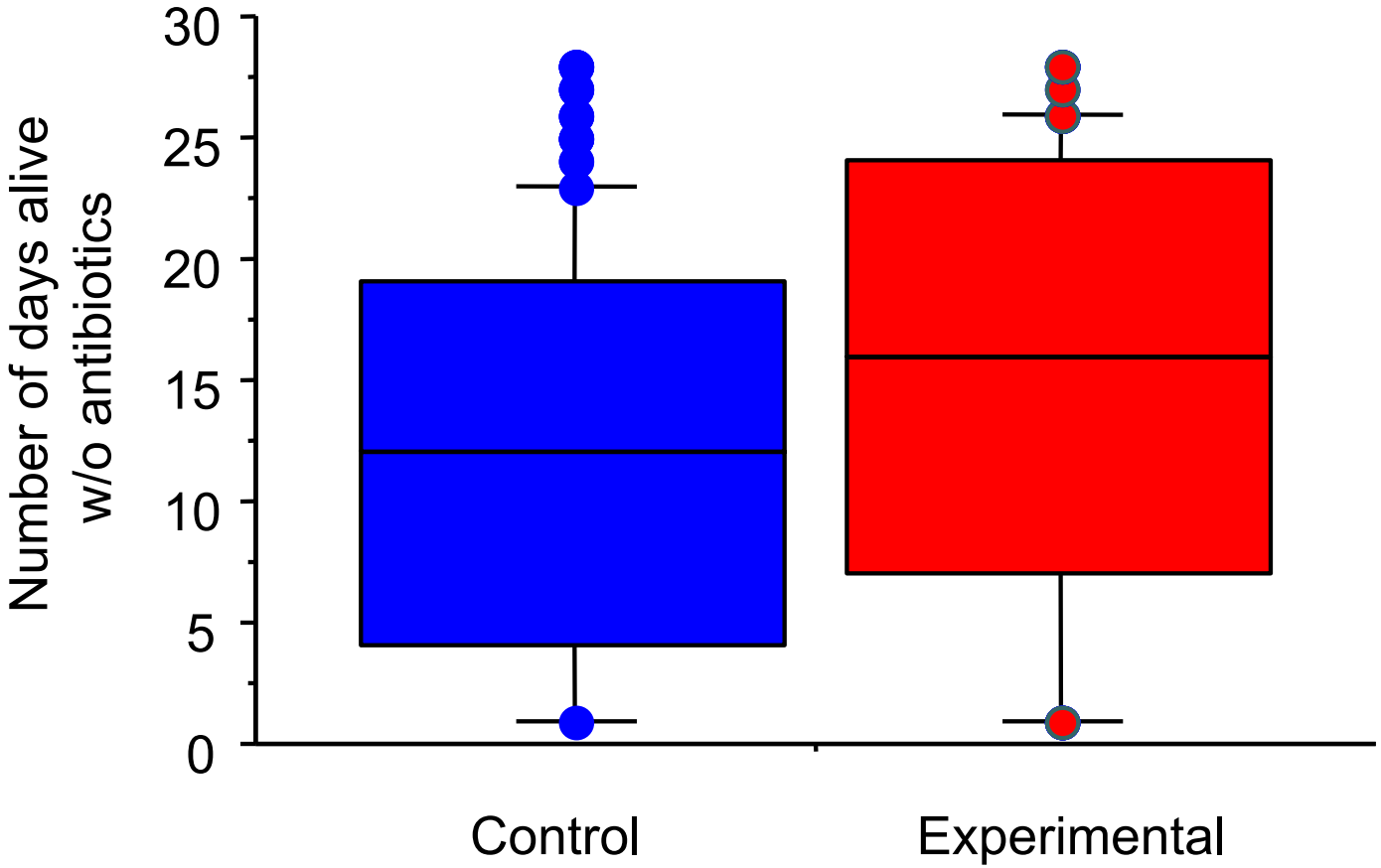
Rello J, et al Chest 2002;122:2115.

Variable	With VAP	Without VAP	Significance
Mortality	30.4	30.6	N.S.
Duration of MV	14.3±15.5	4.7±7.0	P<0.001
ICU LOS	11.7±11.0	5.6±6.1	P<0.001
Hospital LOS	25.5±22.8	14.0±14.6	P<0.001
Hospital charges	104,983±91,080	63,698±75,030	P<0.001

Numbers of days alive without antibiotics at days 28

Bouadma et al. Lancet 2010;375:463-74

Absolute difference: 2.7 days [95% CI, 1.4–4.1]
Relative reduction in antibiotic exposure: 23%



How to better define clinical success (**failure**) at TOC?

- All patients fulfilling **at least one** of the following conditions should be classified as a **clinical failure**:
  1. Rise in CPIS by at least 2 points on Day 3
  2. Failure of the CPIS to drop by at least 2 points on Day 10
  3. Continuation of antibiotics after Day 10
  4. Restarting antibiotics before the TOC visit; **OR**
  5. The patient **died** before the TOC visit

How to better define clinical **success** at TOC?

- A patient should meet **all 3 conditions** to be classified as "**Clinical success**":
  1. The patient **never** reached any **failure criteria**
  2. Improvement or lack of progression of **chest x-ray** abnormalities
  3. Resolution towards normal of the **CPIS components**, including tracheal secretions (volume and purulence), temperature, blood leukocytes, oxygenation (PaO_2/FiO_2)

Trials in HAP/VAP Patients With Infection Caused by Multiresistant Microorganisms

- **Noninferiority** trials are **NOT** appropriate in this setting:
  1. noninferiority trial design assumes that the active-controlled drug has a known and reliable treatment effect.
  2. the use of the same control antibacterial drug in the comparator arm is not possible.